

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.: 10/657,550 Confirmation No.: 9356
Applicant(s): Chaudry
Filed: 09/04/2003
Art Unit: 1616
Examiner: James Henry Alstraum Acevedo
Title: FORMULATIONS AND METHODS FOR TREATING RHINOSINUSITIS

Docket No.: 048765/277062
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REPLY BRIEF UNDER 37 CFR § 41.41

This Reply Brief is filed pursuant to 37 CFR § 41.41 and is filed in response to the Examiner's Answer of August 15, 2011. These comments are an extension of, and in addition to, the arguments presented in the Appeal Brief filed on June 10, 2011.

Status of Claims.

Claims 2-3, 7-9, 13-21, 26, 31-34, and 36-70 have been canceled. Claims 1, 4-6, 10-12, 22-25, 27-30, 35, 71-77 are pending in the application and all stand rejected as unpatentable over a combination of prior art references as set forth in greater detail below. All rejections of record are appealed herein. Accordingly, claims 1, 4-6, 10-12, 22-25, 27-30, 35, 71-77, which were finally rejected in the Office Action of August 6, 2010, are the subject of this appeal.

Grounds of Rejection to be Reviewed on Appeal.

As stated in the Final Rejection dated August 6, 2010, claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE from the

online Physician's Desk Reference , as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lippy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) (hereinafter "Flonase") in view of U.S. Patent No. 6,464,958 to Bernini et al. (hereinafter "Bernini"), WO 99/18971 to Harris (hereinafter "Harris"), and U.S. Publication No. 2002/0061281 to Osbakken et al. (hereinafter "Osbakken"). Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over Flonase in view of Bernini, Harris, Osbakken, and further in view of U.S. Patent No. 6,368,616 to Doi (hereinafter "Doi") and U.S. Patent No. 6,608,054 to Meade (hereinafter "Meade"). Claims 75-76 stand rejected under 35 U.S.C. §103(a) as being obvious over Flonase in view Bernini and Osbakken, and further in view of "Management of Allergic Rhinitis", Nursing Times, 2003, 99(23), Abstract to Walker (hereinafter "Walker") and "Topical Antiviral Agents for Herpes Simplex Virus Infections", Drugs Today, 1998, 34(12), Abstract to Hamuy et al. (hereinafter "Hamuy"). These are the only rejections in this appeal.

As explained more fully below, Appellant submits that the claims as grouped in the final rejection do not stand or fall together. There are several independent reasons why the claims are patentable over the cited prior art. Thus, Appellants have grouped the grounds of rejection as follows:

- 1) The rejection of claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 under 35 U.S.C. §103(a) as being obvious over any combination of Flonase, Bernini, Harris, and Osbakken;
- 2) The rejection of claims 71-74 under 35 U.S.C. §103(a) as being obvious over any combination of Flonase, Bernini, Harris, Osbakken, Doi, and Meade; and
- 3) The rejection of claims 75-76 under 35 U.S.C. §103(a) as being obvious over any combination Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy.

Argument

- (1) **Claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 are not obvious over any combination of Flonase, Bernini, Harris, and Osbakken.**

Claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 stand rejected under 35 U.S.C. §103(a) as being obvious over any combination of Flonase, Bernini, Harris, and Osbakken.

The Examiner argues that it would have been obvious to modify the Flonase formulation to (1) include an antifungal agent and (2) to modify the particle size distribution of the fluticasone particles found in the Flonase formulation. With regard to the modification of the Flonase particle size distribution, the Examiner argues that optimization of particle size distribution is routine in the art and, therefore, is not patentable.

Appellant notes that pursuant to MPEP 2144.05, that a showing of criticality can rebut a *prima facie* case of obviousness. That is, evidence of unexpected results of the claimed invention can be used to overcome an obviousness rejection. The Examiner, however, attempts to belittle and dismiss the nature of the study carried out concerning the claimed particle size distribution. For instance, the Examiner appears to have provided no weight to the study comparing the currently claimed particle size distribution with that of Flonase because the data is based on individual's journal ratings, error bars were not included at the time of the study, and the use of ANOVA. That is, the Examiner appears to be "fishing" for excuses to not consider real data showing the unexpected benefits provided by the currently claimed invention.

As discussed more detail below, formulations including the currently claimed formulations were compared to Flonase. The recited particle size distribution of the currently claimed formulations was the only difference from the Flonase formulation. Surprisingly, the recited particle size distribution has been shown to provide individuals with an increased reduction in the total symptoms of rhinitis as compared to the results realized by individuals receiving the same amount of active from Flonase.

Upon comparison of the reported particle size distribution of Flonase (as provided with the Appeal Brief) with the currently claimed distributions, one skilled in the art can quickly identify that the particle size distribution of Flonase generally contains larger particles and a wider distribution of particles. For instance, about 50% of the particles in Flonase are greater than 4.7 microns. To the contrary, the currently claimed invention recites that about 90% of the fluticasone particles are less than 5.3 microns. Accordingly, one skilled in the art would need to significantly reduce the average particle size used in the Flonase formulation to even begin to approach the currently claimed particle size distribution. Such a modification, however, would

require a substantial alteration of the overall particle size distribution of Flonase without any teaching or rational basis for making such a drastic change.

Furthermore, the reported D50 level for Flonase is roughly 3 times larger than that of the currently claimed distribution (i.e., 4.7 microns as compared to the currently recited 1.5 micron rating). This gross disparity is yet one more example of the considerable gap between the Flonase particle size distribution and the claimed distribution. Accordingly, the Flonase particle size distribution is quite different than the currently claimed particle size distribution in several respects and Appellant submits that one skilled in the art would have no rational basis for modifying the Flonase distribution by generally reducing the average particle size to 1/3 of its present formulation.

Generally speaking, one skilled in the art would have no rational basis for modifying Flonase to have the particular particle size distribution recited in each of the currently pending independent claims. **Such a modification would require a substantial alteration of the Flonase particle size distribution, particularly considering the lack of any teaching in the art to make such a modification.** Additionally, Appellants note that the mere possibility that the Flonase particle size distribution could be modified in such a way does not mean that such a modification would have been obvious to the skilled artisan, particularly in view of no teaching in the art that such a modification would provide the surprising results discussed below.

Appellants note that the Example 6 of the present specification and Figs. 1-4 (all of which has been amended into the present application from a parent application as discussed above in the response filed on January 6, 2011 and entered by the Examiner in the Advisory Action dated January 21, 2011) provides a direct comparison between the currently claimed particle size distribution and Flonase (the only available Fluticasone product at the time of the currently claimed invention). See Example 6 of the present specification (as amended into the present specification as discussed above). As explained in Example 6, the “low dose” designation refers to the number of sprays including fluticasone received by patients. “Low dose” groups only received 1 spray of fluticasone per nostril in a day. Comparison of the Dey FP Low Dose Group with the Flonase Low Dose Group shows that the currently claimed invention provides a notable and surprising improvement from the symptoms of SAR despite both groups receiving the

same amount of active. Table 1, provided below, provides an approximate quantitative value for the improved relief from the symptoms of SAR realized by patients in the Dey FP Low Dose group.

Table 1

Day	Dey FP Low Dose Group – approximate LS value	Flonase Low Dose Group – approximate LS value	% Improvement in TNSS over the Flonase Low Dose Group
2	-2.9	-2.1	~38%
3	-4.2	-3.3	~27%
4	-4.7	-3.9	~20%
5	-5.2	-4.7	~11%
6	-5.3	-4.4	~20%
7	-5.9	-4.5	~31%
8	-5.8	-5.1	~14%
9	-6.3	-5.8	~9%
10	-6.8	-6.2	~10%
11	-7.4	-5.6	~21%
12	-7.4	-6.1	~19%
13	-7.4	-6.2	~19%
14	-7.8	-6.5	~20%

Appellant submits that one skilled in the art (and one suffering from the symptoms of seasonal allergic rhinitis) would recognize the aforementioned percentages of TNSS improvement as not merely a minor difference of degree as suggested by the Examiner. Appellant notes that the patients in the Dey FP Low Dose group realized these improved reductions in TNSS while receiving the same amount of fluticasone as the patients in the Flonase Low Dose group. **This result is surprising because one skilled in the art would expect the same results (i.e., magnitude in relief of the symptoms) from both groups since both groups received the same amount of fluticasone. Again, the only difference in the Dey FP and**

Flonase formulations is the respective particle size distributions. As such, the currently claimed particle size distribution provides unexpected results. These results provide further evidence of the non-obviousness of the currently claimed invention.

Finally, Appellant notes that none of the secondary references (alone or in any combination with Flonase) cure the deficiencies of Flonase or negate the criticality of the claimed particle size distributions.

As discussed above, the currently claimed particle size distribution does achieve unexpected results. Therefore, Appellants submit that the Examiner is in error for disregarding the showing of unexpected results establishing criticality of the claimed particle size distribution as mere routine optimization.

(2) **Claims 71-74 are not obvious over any combination of Flonase, Bernini, Harris, Osbakken, Doi, and Meade.**

Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over any combination of Flonase, Bernini, Harris, Osbakken, Doi, and Meade.

Claims 71-74 recite the addition of particular complexing agents. As such, the Examiner cites Doi for teaching suspensions for nasal applications containing citric acid and EDTA and Meade for teaching that sodium edetate and citric acid are known complexing agents.

As discussed above, Flonase, Bernini, Harris, and Osbakken (alone or in any combination) do not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail above. Appellants submit that the addition of Doi and/or Mead do not cure the noted deficiency of any combination of Flonase, Bernini, Harris, and Osbakken. More specifically, Flonase, Bernini, Harris, Osbakken, Doi, and Meade (considered alone or in any combination) do not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail above. For at least this reason, claims 71-74 are not obvious over any combination of Flonase, Bernini, Harris, Osbakken, Doi, and Meade.

(3) **Claims 75-76 are not obvious over any combination of Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy.**

Claims 75-76 stand rejected under 35 U.S.C. §103(a) as being obvious over any combination Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy.

Claims 75-76 recite specific combinations of several active agents including fluticasone having the particular particle size distribution shown to beneficially exhibit unexpected results.

The Examiner cites Walker and Hamuy to propose that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are well-known anti-viral agents (Hamuy).

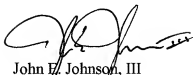
As discussed above, Flonase, Bernini, Harris, and Osbakken (alone or in any combination) do not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail above. Appellants submit that the addition of Walker and/or Hamuy do not cure the noted deficiency of any combination of Flonase, Bernini, Harris, and Osbakken. More specifically, Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy (considered alone or in any combination) do not teach, suggest, or otherwise render predictable the recited particle size distribution characterized by 5 distinct levels shown to beneficially exhibit unexpected results as discussed in greater detail above. For at least these reasons, claims 75-76 are not obvious over any combination of combination Flonase, Bernini, Harris, Osbakken, Walker, and Hamuy.

CONCLUSION

In light of the foregoing reasons, as well as those presented in Appellant's Appeal Brief, Appellant respectfully submits that the claims of record are patentable over the cited references. As a result, it is respectfully requested that the Board of Patent Appeals and Interferences reverse the final rejection of the pending claims.

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